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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,807	04/25/2006	Marc Port	3493-0156PUS1	9005

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
11/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,807	PORT ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-20* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/10/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 9/10/2010, in reply to the Office Action mailed 3/11/2010, is acknowledged and has been entered. Claims 1 and 2 have been amended. Claims 1-9 and 12-20 are pending, of which claims 5-7 and 14-20 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1-4, 8, 9, 12 and 13 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but they are not persuasive for reasons set forth herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 8, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter (US 6,656,448) in view of Odake (US 5,100,874).

Carpenter discloses MRI contrast agents comprising one or more matrix metalloproteinase inhibiting targeting moieties attached to one or more paramagnetic metal ions, further comprising an optional linking moiety, L_n, between the targeting moieties and the paramagnetic metal ions. The paramagnetic metal ions are present in the form of metal complexes or metal oxide particles (column 45, lines 24+). Iron is described as suitable paramagnetic metal. The pharmaceuticals have the formulae, $(Q)_d$--L_n—$(C_h$--$X)$, $(Q)_d$--L_n --$(C_h$-$X_1)_{d'}$, **$(Q)_d$--L_n--$(X_2)_{d''}$**, and $(Q)_d$--L_n--(X_3), wherein Q represents a compound that inhibits a matrix metalloproteinase, d is 1-10, d'=1-100, L_n represents an optional linking group, C_h represents a metal chelator or bonding moiety, X represents a radioisotope, X_1 represents paramagnetic metal ion, X_2 represents a paramagnetic metal ion or heavy atom containing insoluble solid particle, d" is 1-100, and X_3 represents a surfactant microsphere of an echogenic gas (column 46, lines 1-28). Suitable MMP inhibitors include peptides, etc. (column 46). With regard to the targeting ligand, a functional group, such as --CONH--, OH, --COOH, or --SH, is

necessary for a molecule to be an effective inhibitor of MMPs. This functional group is involved in the chelation of the active site zinc ion, and is commonly referred to as the zinc binding group or ZBG. The hydroxamate, for example, is a bidentate ligand for zinc (column 46, lines 10-20). See also column 46-50, including succinyl hydroxamates and alanine hydroxamates as inhibitors. There are three key features of the pharmaceuticals that determine their efficacy: MMP selectivity, inhibitory potency, typically expressed as the K_i value, and the rate of clearance from the blood. Preferred pharmaceuticals of the present invention are comprised of inhibitors, Q, which exhibit selectivity for MMP-1, MMP-2, MMP-3, MMP-9, or MMP-14 alone or in combination over the other MMPs. Most preferred are comprised of inhibitors, Q, which exhibit selectivity for MMP-2, MMP-9, or MMP-14 alone or in combination over the other MMPs. K_i values for the preferred pharmaceuticals of the present invention are <100 nM for one or more of MMP-1, MMP-2, MMP-3, MMP-9, or MMP-14. K_i values for the most preferred pharmaceuticals of the present invention are <10 nM for one or more of MMP-2, MMP-9, or MMP-14.

A number of methods can be used to attach the MMP inhibitors, Q, to paramagnetic metal ion or heavy atom containing solid particles,X_2, by one of skill in the art of the surface modification of solid particles. In general, the targeting moiety Q or the combination $(Q)_d L_n$ is attached to a coupling group that react with a constituent of the surface of the solid particle. The coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface and can also include polyphosphonates, polycarboxylates, polyphosphates (column 53).

The imaging agents targeted to one or more MMP's would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, atherosclerosis and other degradative disease processes. These imaging agents, containing a ligand directed at one or more MMP's (e.g. MMP-1, MMP-2, MMP-3, MMP-9), will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases (column 3, lines 51+).

Carpenter does not specifically recite that hydroxamic tetrapeptide derivatives, such as p-aminobenzoy-Gly-Pro-D-Leu-Dala-NHOH is used as the MMP targeting ligand.

Okane discloses peptide derivatives having specific inhibitory activity against collagenases (abstract). Abnormal overaction of collagenases is shown in processes of destruction and repair of tissues, and is observed for example in cases such as rheumatoid arthritis, periodontal diseases, etc. Inhibition of collagenases provides a useful means for treating such diseases (column 1, lines 1-22). New peptide compounds which selectively inhibit the action of collagenases derived from vertebrates without inhibiting other protease actions (i.e. exhibit an inhibitory action of high specificity), and which have low toxicity, improved metabolic rate are disclosed, including peptidylhydroxamic acid derivatives of general formula X^1-X^2-X^3-X^4-NHOH (column 1, lines 45+). In particular, p-aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH is disclosed (claim 6). See also claim 1. Inhibitory activity against collagenases is disclosed in Tables 1 and 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ the hydroxamic acid tetrapeptide derivatives of Okane as MMP inhibitor (Q) in the compounds and methods of Carpenter, such as $(Q)_d$--L_n--$(X_2)_{d''}$, wherein Q represents a compound that inhibits a matrix metalloproteinase, L_n represents an optional linking group, and X_2 represents a paramagnetic metal ion containing insoluble solid particle (iron oxide). For example, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the hydroxamic acid tetrapeptide derivatives, such as aminobenzoy-Gly-Pro-D-Leu-D-Ala-NHOH as functional equivalent to succinyl hydroxamates and alanine hydroxamates as inhibitors disclosed by Carpenter. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143. In the instant case, the substituted components and their functions were known in the art at the time of the instant invention. One of ordinary skill in the art could have substituted one known MMP (collagenase) inhibitor for another, and the results of the substitution would have been predictable, that is effective conjugation of the MMP inhibitor to a diagnostic moiety for targeting MMP in localized imaging methods.

Claims 1-4, 8, 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter (US 6,656,448) in view of Odake (US 5,100,874), further in view of Portet (*J. Colloid Interfac. Sci.*, 2001, 238, p. 37-42).

The rejection over Carpenter in view of Odake is applied as above. It would have been further obvious to provide bis-phosphonate coating on iron oxide particles used as diagnostic moiety when the teachings of Carpenter and Odake are taken in view of Portet.

Portet discloses iron oxide nanoparticles as contrast agents in magnetic resonance imaging. Bisphosphonate coating on iron oxide provided the most stable coating in a wide range of pH, including neutrality, in comparison to carboxylates, sulfonates, etc.(abstract, page 42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide iron oxide particles coated with gem-bisphosphonate as the diagnostic moiety (paramagnetic metal ion oxide particle) in the compositions of Carpenter for use in targeted MRI imaging of MMP (collagenase) activity. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Portet teaches that bisphosphonate coated iron oxide particles are efficiently stabilized (page 42). In addition, Carpenter teaches that in synthesis, the coupling groups can be any of a number of silanes which react with surface hydroxyl groups on the solid particle surface and can also include polyphosphonates, polycarboxylates, polyphosphates (column 53).

Applicant argues on pages 7-11 of the Response that the problem to be solved was to find specific targeting ligands capable of effectively targeting MMP in vivo, and submit that the Examiner's rejection appears to be the result of hindsight that has arisen by piecing together some logic using the disclosure of the instant specification. Applicant asserts that the skilled artisan would not have contemplated using the peptides described in Odake and have a reasonable expectation of success in doing so for the reasons that 1) a huge number of potential MMP targeting entities exist; 2) it was not obvious to believe that the affinity of the peptide toward MMP would be preserved in tissue; 3) Odake describes only therapeutic use of the peptides and 4) it was surprising that the product according to the instant invention would be effectively efficient in view of the very low level of MMP target.

This is not found to be persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, it was known in the art to conjugate MMP targeting ligands, including peptide to signaling entities for medical imaging, as shown by Carpenter. It was known from Odake that p-aminobenzoyl-Gly-Pro-D-Leu-D-

Ala-HNOH is an MMP inhibitor. Therefore, the rejection relies only upon knowledge which was within the level of ordinary skill at the time the claimed invention was made and is considered to be proper.

With regard to the arguments that there are a large number of potential MMP targeting entities, and that there is a large gap between theoretical affinity of a MMP ligand (biovector) in vitro and its real and actual efficiency, it is noted that obviousness does not require absolute predictability, however, at least some degree of predictability is required. See MPEP 2143.02. II. In the instant case, the peptides of Odake have demonstrated collagenase inhibition in vitro, are intended for use in vivo, therefore one would have had at least a reasonable expectation of success in extrapolating the in vivo efficacy of the peptides toward MMP inhibition in vivo.

With regard to the argument that Odake only describes the therapeutic use of the peptides, it is noted that In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the rejection relies upon a combination of Carpenter and Odake, and the Carpenter reference provides ample teaching of diagnostic applications of MMP inhibitors.

With regard to the argument that it was surprising that the product according to the invention would be effectively efficient in view of the very low level of MMP target, such as MMP concentration in targeted atherosclerotic tissue, and that experiments

with compound B / P947 provide data which demonstrate the effectiveness of the presently claimed invention which could not be predicted, such that coupling with contrast moiety did not alter the properties of the peptides, see MPEP 716.02(d). It is noted that allegations of unexpected results must be commensurate in scope with the claimed invention. Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (Claims were directed to a process for removing corrosion at "elevated temperatures" using a certain ion exchange resin (with the exception of claim 8 which recited a temperature in excess of 100C). Appellant demonstrated unexpected results via comparative tests with the prior art ion exchange resin at 110C and 130C. The court affirmed the rejection of claims 1-7 and 9-10 because the term "elevated temperatures" encompassed temperatures as low as 60C where the prior art ion exchange resin was known to perform well. The rejection of claim 8, directed to a temperature in excess of 100C, was reversed.). See also *In re Peterson*, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an

obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the *prima facie* case because experiments limited to sodium were not commensurate in scope with the claims.). In the instant case, applicant alleges unexpected results only for compound B / P947 which is a specific peptide coupled to a specific contrast moiety. However, the claims are broad and are readable upon any of hundreds of possible peptide sequences and *any* signal moiety (i.e. which could include any of microbubles or liposomes for ultrasonic imaging; fluorescent dyes for optical imaging; nanoparticles or chelate for MRI; barium sulfate or iodinated compounds for CT imaging; etc. among others...), therefore the claims are not commensurate in scope with the compound for which unexpected results are alleged.

Conclusion

No claims are allowed at this time.

Although Applicant's arguments as set forth in the aforementioned Response have been fully considered, they are deemed unpersuasive. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS